Int.J.Curr.Microbiol.App.Sci (2018) *7*(2): 3824-3832

International Journal of Current Microbiology and Applied Sciences
***ISSN: 2319-7706* Volume 7 Number 02 (2018)**
Journal homepage: http://www.ijcmas.com

Original Research Article https://doi.org/10.20546/ijcmas.2018.702.453

A Study on the Microbial Profile of Pyrexia of unknown origin from inpatients of Tertiary Care Hospital in Chennai

P. Shanmugapriya[1], A. V. M. Balaji[2]*, K. Subha[2], Dheepa Manoharan[2] and Selvi[2]

[1]Department of Microbiology, Thanjavur Medical College, Thanjavur, Tamil Nadu, India
[2]Department of Microbiology, Stanley Medical College, Chennai, Tamil Nadu, India

**Corresponding author*

Keywords

clinical syndrome, Thermometer, knowledge, fever, etiologies, elucidation

Article Info

Accepted:
04 January 2018
Available Online:
10 February 2018

A B S T R A C T

Fever could have many causes including infective and non infective origin. PUO is a clinical syndrome that may result from much common aetiology which was characterized by prolonged fever without the signs or symptoms indicative of a well defined disease process. The aim of the study to find the infectious causes of fever by microscopy, serology and culture methods, to compare quantitative buffy coat vs peripheral smear study for the detection of malarial parasite and to find out Antimicrobial Susceptibility pattern of the organisms isolated. Among the 125 patients selected 66 were males and 59were females. The causes of Pyrexia of unknown origin were Infectious in 62.4%, Collagen disorder in 3.2%, Neoplasm in 2.4%, Miscellaneous in 6.4% and undiagnosed in 25.6% of patients. In Infectious causes chronic urinary tract infection was the commonest cause (12.8%) followed by malarial fever (11.2%), Leptospirosis (10.4%), enteric fever (8.0%), hepatitis (6.4%), tuberculosis (5.6%) and less frequently acquired immuno deficiency syndrome (1.6%), pancreatitis (1.6%), viral meningitis (1.6%), Rheumatic fever (0.8%), filariasis (0.8%), sinusitis (0.8%) and liver abscess (0.8%) were documented the source of PUO in the selected group. In 62.4% of cases with fever more than 3 weeks were caused by infectious origin. Causes were unknown in 25.6% of patients.UTI was the most common cause in infectious origin.QBC is more sensitive to detect malarial parasite than Peripheral smear study. The sensitivity of Detection in Leptospiral aetiology by MSAT were high compared with IgM ELISA. Brucellosis, granulomatous diseases and certain neoplastic disorders would have contributed to the undiagnosed group in the diagnosis of PUO.

Introduction

Pyrexia of unknown origin (PUO) continues to be one of the most challenging situations faced by clinicians (Barbado *et al.*, 1992). Fever is a symptom as a result of infective and non infective origin. Despite advances in the knowledge and development of many advanced diagnostic techniques, one still encounters instances of fever that cannot be readily explained the source of origin (Emanuel Appelbaum *et al.*, 1967). The clinical importance of fever started at Eighteenth century by the invention of

Thermometer by Gabriel Daniel Fahrenheit (Welsby, 1985).

PUO is a clinical syndrome that may result from much common etiologies which is characterized by prolonged fever without the signs or symptoms of indicative of a well defined disease process (Masashi Goto *et al.*,). PUO, as defined by Petersdorf and Beeson in 1961, includes illness persisting for 3 weeks or more, occasional episodes of a fever of 38.3°C (101°F) or more, and an unclear cause upon examination after one week of hospitalization (Yayoi Iikuni *et al.,* 1994).

A systematic approach to its elucidation includes a careful history, frequent physical examination, four-hourly records of temperature and pulse rate monitoring is needed (Effersoe, 1969).

So this current study was conducted to find out the Microbial profile of pyrexia of unknown origin from inpatients of Tertiary care hospital.

Materials and Methods

This Prospective study was conducted in the department of Microbiology in association with clinical departments in Tertiary care hospital in Chennai from January 2017 to June 2017. Ethical committee clearance and Informed consent from the patients in their local language were obtained. In patients with undiagnosed fever for more than 3 weeks duration were included in this study.

Among the 125 patients selected for this study, samples such as blood and urine were collected aseptically. Other clinical specimens like Sputum, Pus, Cerebrospinal fluid and Stool were collected from appropriate cases.

Blood culture was done using Brain heart infusion broth. A patient with suspected Rheumatic fever on clinical grounds three blood cultures were taken with 30 minutes interval to rule out impending infective endocarditis. Throat swab was also taken for the same patient for bacterial culture. ASO titration was also done to support streptococcal aetiology.

Quantitative buffy coat and Peripheral smear study was done to detect malarial parasite and microfilaria.

Serum was tested for Salmonella infection by Widal (tube agglutination test) using King Institute antigen.

For the diagnosis of Leptospira, MSAT (done at Leptospira reference laboratory, Chennai) and IgM antibody ELISA (SD Bioline) were done.

HIV testing was done according to NACO guidelines (Strategy III).

Urine and Pus samples were processed for aerobic bacterial culture and antimicrobial sensitivity test done for the isolates.

Sputum samples were processed for Mycobacterial infection by Acid fast staining and aerobic culture on LJ medium.

CSF sample were processed for Cryptococcus by negative staining, for Mycobacteria by acid fast staining, aerobic culture in LJ medium and for fungal origin to be processed in Sabouraud's dextrose agar and aerobic bacterial culture were also performed.

Among the 125 cases selected in this study there have been a past history of meningitis in one, meningioma which was operated in one and also meningomyelocele operated in one patient were present and the reason for CSF samples were processed in each of the infective origin.

For all the patients chest roentgenogram and electrocardiogram were taken.

On the clinical suspicion of PUO, collagen vascular disorder, liver pathology and malignant aetiology were screened by appropriate specimens and the results were correlated on other clinical investigation like CT scan, USG and Biopsy.

Depending upon the need, specialized investigations like ultrasonography (USG), echocardiography, CT scan and tissue biopsies were also carried out. Results were analyzed as follows.

Results and Discussion

Among the 125 patients selected 66 were males and 59 were females.

Among the co-morbid diseases, diabetes mellitus and hypertension play an important role and less commonly by chronic kidney disease, coronary artery disease and hypothyroid state. *Pemphigus vulgaris* and cirrhosis with portal hypertension were also seen in one patient each. A patient with collagen disorder (SLE) developed nephrotic syndrome who had Ascaris worms passed in vomitus and eggs were demonstrated in stool samples.

Infections were the most common cause (62.4%) of PUO. This is similar to the study conducted by Kashiwagi *et al.,* (1986) in which infections accounted for 55.0% cases of PUO.

Among the infections, chronic urinary tract infection was the commonest cause(12.8%) followed by malarial fever (11.2%), Leptospirosis (10.4%), enteric fever (8.0%), hepatitis (6.4%), tuberculosis (5.6%) and less frequently acquired immuno deficiency syndrome (1.6%), pancreatitis (1.6%), viral meningitis (1.6%), Rheumatic fever (0.8%), filaria (0.8%), sinusitis (0.8%) and liver abscess (0.8%) were documented as a cause of PUO in selected patients.

Urinary Tract Infection was present in 12.8% of patients. This current study had discordant results with the results of Iikuni *et al.,* (1994) in which 1.3% of patients with PUO had UTI. This high incidence may be explained due to recurrent infection with predisposing factors like DM, CKD in this study group.

In the origin of UTI, *Escherichia coli* (9/16) was the commonest organism isolated which shows Extended Spectrum Beta Lactamases (ESBL) production in 44.4% (4 out of 9) of the isolates seconded by *Klebsiella pneumoniae* (3/16) which shows 100 % production of ESBL were sensitive to Imipenam. ESBL non producers were responded well to cefotaxime and gentamicin.

Enterococci (2/16) were isolated in 12.5 % of urine culture and sensitive to vancomycin. High level aminoglycoside resistance were screened by 120µg gentamicin disk found to be negative. These strains were responded to penicillin and amikacin combination.

Staphylococcus aureus (1/16) were isolated in 6.25% of urine culture which were sensitive to methicillin and clinical improvement with ceftriaxone.

Coagulase negative *Staphylococcus* (1/16*)* were isolated in 6.25% of urine culture which was found to be Methicillin resistant (100%). Patient clinical condition improved with administration of amikacin and vancomycin after the sensitivity results, which was not shown by ceftriaxone during the time of admission.

Malarial fever was the next common (11.2%) infectious cause followed by the bacterial

origin, which was correlated with study conducted by Jung *et al.,* (1999) in which 9% of PUO were caused by malaria. By Quantitative buffy coat method ring form of malarial parasite were detected in 73.3% (11/15) and Falciparum gametocytes in 20% (3/15). The results were correlated with Peripheral smear study, in which ring forms in 50% (3/6) and Falciparum gametocytes in 33.3% (2/6), in the detection of malarial parasite. QBC has high sensitivity compared with Peripheral smear study. This could be due to centrifuging the samples and use of fluorescence microscope in QBC process. Moody *et al.,* (2002) study documented that QBC was more sensitive method than the peripheral smear study. Patients diagnosed to have malaria responded to artemisinin-based combination therapies.

Leptospirosis was the third common (10.4%) cause in infectious origin. IgM antibody to Leptospira was positive in eleven patients. MSAT was positive in thirteen patients. This equivocal results could be due to the serovars used in MSAT were based on the endemicity of infection and in ELISA the serovars used are as per SD Biolineguidelines. Study conducted by Angela P. Brandao *et al.,* (1998) showed that, the sensitivity of IgM ELISA was lower in comparison with MSAT.

Enteric fever was the fourth common (8.0%) cause in infectious origin. The results were same as the study by Kejariwal and Chakraborti *et al.,* (2001) in which 5.0% of PUO were caused by enteric fever. All patients were responded to ceftriaxone. *Salmonella paratyphi A* was isolated from blood culture from a patient which were sensitive to ciprofloxacin and ceftriaxone.

Viral hepatitis were seen in 6.4% of patients in which HBV was the common source and HCV was less prevalent. This correlated with Shin'ichi Shoji *et al.,* (1994) study, in which 2.5% of PUO were caused by viral hepatitis.

Tuberculosis was diagnosed in 5.6% of patients. Among them five were sputum AFB positive, one was radiologically diagnosed (sputum AFB negative) and one was diagnosed to have TB meningitis by culture methods. This correlated with study by Shin'ichi Shoji *et al.,* (1994) and Yayoi Iikuni *et al.,* (1994) in which tuberculosis was diagnosed in 7.1% and 10% of PUO cases respectively. CSF showed growth of Mycobacterium tuberculosis after 4 weeks of incubation in LJ medium in a patient with meningitis. That patient was empirically started on ATT by cytological and radiological findings. He responded very well and the diagnosis correlated with our culture reports.

HIV reactivity was present in two (1.6%) of PUO patients. This correlates with study by Jung *et al.,* (1999) in which 0.4% of PUO were caused by HIV.

Viral meningitis was diagnosed in 1.6% of PUO patients by CSF analysis for whom bacterial, fungal and mycobacterial culture were found to be negative. This was correlated with Shin'ichi Shoji *et al.,* (1994) in which 1% of PUO were caused by viral meningitis.

Pancreatitis was diagnosed in 1.6% of PUO patients.

ASO titre was above 300 todd units in a patient who had fever with migrating polyarthritis. Blood cultures were found to be negative on three occasions. He responded very well to penicillin.

Microfilaria was detected in one alcoholic patient (0.8%) by QBC and peripheral smear. Fever subsided with Diethyl carbamazine treatment.

Table.1 Details of positive investigation profile of fever (n=125)

Investigation		No of cases
Quantitative buffy coat (n=15)	Ring form	11
	Falciparum Gametocyte	3
	Microfilaria	1
	Total	15
Peripheral smear (n=6)	Ring form	3
	Falciparum gametocyte	2
	Microfilaria	1
	Total	6
IgM Leptospira (n=11)	Positive	11
MSAT (n=13)	Positive	13
Widal agglutination (n=10)	H-200, O-200 titre	9
	AH-200, O-200 titre	1
	Total	10
ASO titre (n=1)	>300todd units	1
HIV (n=2)	Reactive	2
HBV (n=7)	HBsAg positive	7
HCV (n=1)	Anti HCV Ab positive	1
SLE (n=2)	ANA positive	2
Sputum AFB (n=5)	Positive	5
CSF Mycobacterial culture (n=1)	*Mycobacterium tuberculosis*	1
Blood culture (n=1)	*Salmonella paratyphi A*	1
Urine culture (n=16)	*Escherichia coli*	9
	Klebsiella pneumoniae	3
	Enterococci	2
	Staphylococcus aureus	1
	Coagulase negative Staphylococcus	1
	Total	16

Table.2 Sensitive pattern among urine culture isolates

Organism	Total no of isolates	Sensitivity pattern	No of isolates
Escherichia coli	9	ESBL	4 (44.4%)
		Non ESBL	5 (55.6%)
Klebsiella pneumoniae	3	ESBL	3 (100%)
		Non ESBL	0 (0%)
Enterococci	2	HLAR	0 (0)%
		Vancomycin resistant	0(0%)
		Vancomycin sensitive	2(100%)
Coagulase negative *Staphylococcus*	1	Methicillin resistant	1 (100%)
		Methicillin sensitive	0 (0%)
Staphylococcus aureus	1	Methicillin resistant	0 (0%)
		Methicillin sensitive	1 (100%)

(Abbreviation-ESBL-Extended spectrum betalactamase, HLAR-High level aminoglycoside resistance).

Table.3 Diagnosis by other modalities

Method		Diagnosis	No of patients
Radiology	Chest X ray	Tuberculosis	6 (5 were sputum AFB positive)
	Ultrasound	Liver abscess	1
	CT scan	Pancreatitis	2
		Sinusitis	1
		Pituitary tumour	1
Pathology	Biopsy	Squamous cell carcinoma lung	1
		Adenocarcinoma lung	1
Biochemistry & Pathology	CSF analysis	Viral meningitis	2
Clinical diagnosis	Chloroquine response fever	Clinical malaria (not evident by QBC, Peripheral smear)	8

Table.4 Final diagnosis of 125 patients with PUO

Aetiology		No of cases	Percentage
Infections (n=78) (62.4%)	Malaria	14	11.2%
	Filaria	1	0.8%
	Leptospirosis	13	10.4%
	Enteric fever	10	8.0%
	Rheumatic fever	1	0.8%
	HIV	2	1.6%
	Hepatitis-HBV & HCV	8	6.4%
	Tuberculosis	7	5.6%
	Chronic urinary tract infection	16	12.8%
	Pancreatitis	2	1.6%
	Sinusitis	1	0.8%
	Liver abscess	1	0.8%
	Viral meningitis	2	1.6%
Collagen vascular disease (n=4) (3.2%)	SLE	2	1.6%
	Vasculitis	2	1.6%
Neoplasm (n=3) (2.4%)	Squamous cell carcinoma of lung	1	0.8%
	Adenocarcinoma of lung	1	0.8%
	Pituitary tumour	1	0.8%
Miscellaneous (n=8) (6.4%)	Chloroquine response fever	8	6.4%
Undiagnosed (n=32) (25.6%)		32	25.6%
Total		**125**	

Fig.1 *Plasmodium falciparum* gametocyte in QBC

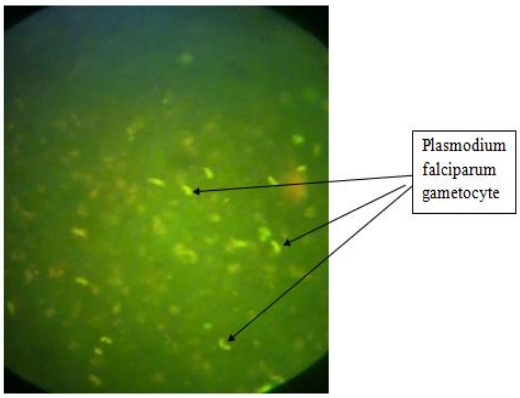


Fig.2 CSF culture on LJ medium showing colonies of *Mycobaterium tuberculosis* from a patient with meningitis

Fig.3 Microfilaria in QBC

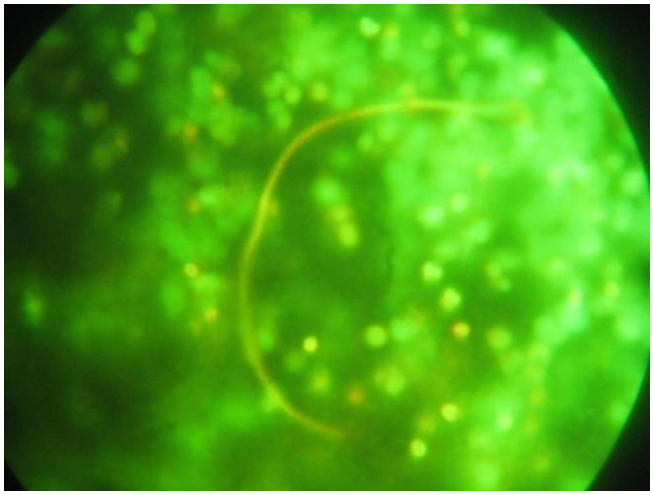
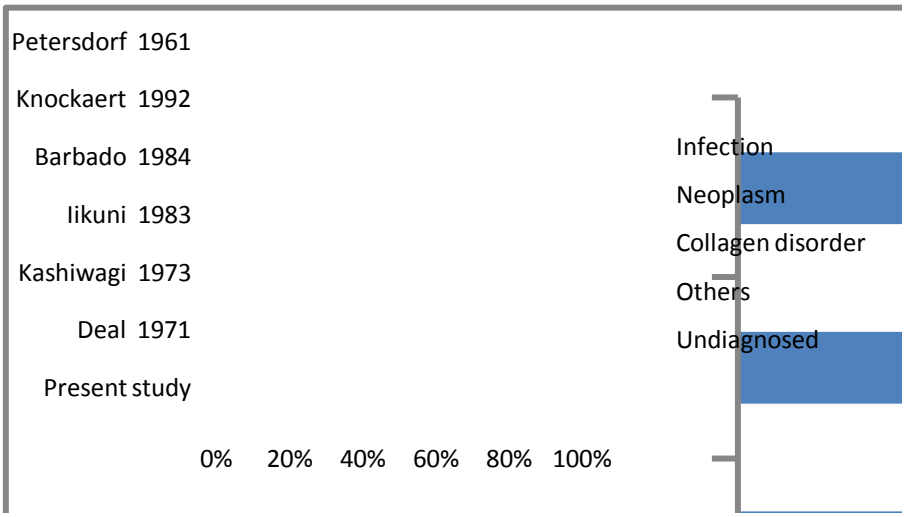


Fig.4 A comparison of diagnostic categories of PUO reports



Sinusitis was detected as a cause of PUO in 0.8% of patients by radiology.

Liver abscess was diagnosed in 0.8% of PUO patients by USG in the later stage of clinical illness. This was correlated with Robert G Petersdorf *et al.*, in which 2.8% liver abscess was the source of fever which was not diagnosed earlier.

Collagen vascular disorder was present in 3.2% of PUO cases. Systemic lupus erythematosis were present in 1.6% of cases. Anti nuclear antibodies were detected by Indirect immunoflorescence technique. Vasculitis were present in 1.6% of cases. This study was correlated with study by Reid *et al.*, (1956) 1.8% of PUO were due to collagen disorder.

Squamous cell carcinoma of lung and adenocarcinoma of lung were detected by biopsy in one patient each as a cause of PUO. Pituitary tumour was detected in one patient by radiology. Overall 2.4% of PUO were caused by neoplasm. This was correlated by Knockaert *et al.*, (1980) in which 7% of PUO were caused by neoplasm.

In this study 6.4% of PUO patients were clinically suspected as having malaria responded to chloroquine within 48 hrs of treatment. But their QBC and Peripheral smear study were found to be negative. This was correlated with study by Jung *et al.*, who denotes criteria for chloroquine responsive fever as fever touching baseline after a period of 48 hours or more with chloroquine without evidence of malarial parasite or failure of other treatment modalities.

In this study undiagnosed cases of PUO were seen in 25.6% of patients. This was correlated with study by Barbado *et al.*, (1992) in which 21.0% and Deal *et al.*, (1971) in which 20% of cases of PUO were undiagnosed. Out of 32 undiagnosed cases, fever subsided spontaneously in 12 patients may be due to antibiotic therapy or may be due to self limiting prolonged viral illness.

Since this study was mainly focused on the common infectious causes and the corresponding investigations, other rare causes like brucellosis, granulomatous diseases and certain neoplastic conditions would have contributed to the undiagnosed group.

In Conclusion 62.4% of cases with fever more than 3 weeks were caused by infectious origin.UTI was the most common cause in infectious origin. QBC is more sensitive to detect malarial parasite than Peripheral smear study. The sensitivity of Detection in Leptospiral aetiology by MSAT were high compared with IgM ELISA. Brucellosis, granulomatous diseases and certain neoplastic disorders would have contributed to the undiagnosed group in PUO.

References

Angela P. Brandão, Eide D. Camargo, Emilson D. da Silva, Marcos V. Silva, and Rui V. Abrão-Macroscopic Agglutination Test for Rapid Diagnosis of Human Leptospirosis. J Clin Microbiol. 1998 November; 36(11): 3138–3142.

Barbado F. J., *et al.*,-Pyrexia of unknown origin: changing spectrum of diseases in two consecutive series. Postgraduate Medical Journal (1992) 68, Pg-884-887

Deal W B. Fever of unknown origin: analysis of 34 patients. Postgrad Med 50: 182, 1971.

Effersoe- Pyrexia of unknown origin. BMJ-19 July 1969: Pg 128-129

Emanuel Appelbaum *et al.*, – The problem of fever of unknown origin. Bull.N.Y.Acad.Med vol-43: No-10: October 1967

Jung A *et al.*, – Unexplained fever analysis of 233 cases in a referral hospital. Indian journal Med Sci-1999, Dec:53 (12): Pg 535-544

Kashiwagi H. Fever of unknown origin: analysis of 56 cases between 1976 and 1985 and a review of the literatures. Nippon Naikagakkai Zasshi 75; 1214,1986.

Kejariwal, D, S. D. Chakraborti *et al.*,-Pyrexia of unknown origin –A Prospective study of 100 cases-Journal of Post graduate Medicine-2001-vol-47,Issue-2,Pg-104-107

Knockaert D C, Vanneste L J, Vanneste S B, Bobbaers H J. Fever of unknown origin in the 1980s: an update of the diagnostic spectrum. Arch Intern Med:152;51,1992.

Masashi Goto *et al.*,- A Retrospective Review of 226 Hospitalized Patients with fever. DOI: 10.2169/internal medicine.46.6038

Reid J V O BM-Pyrexia of unknown origin. BMJ-7 July 1956: Pg 23-25

Robert G Petersdorf *et al.*,-FUO Revisited. La Jolla and Seattle Pg 41-54

Shin'ichi Shoji *et al.*,-Fever of unknown origin: A Review of 80 patients from the Shin'etsu area of Japan from 1986-1992. Internal Medicine vol-33,No-2 (February 1994) Pg 74-76

Welsby P. D. -Pyrexia of unknown origin sixty years on. Postgraduate Medical Journal (1985) 61, Pg-887-894

Yayoi Iikuni *et al.*,-Current fever of unknown origin 1982-1992. Internal Medicine Vol 33, No.2 (February 1994)

How to cite this article:

Shanmugapriya, P., A. V. M. Balaji, K. Subha, Dheepa Manoharan and Selvi. 2018. A Study on the Microbial Profile of Pyrexia of unknown origin from inpatients of Tertiary Care Hospital in Chennai. *Int.J.Curr.Microbiol.App.Sci.* 7(02): 3824-3832.
doi: https://doi.org/10.20546/ijcmas.2018.702.453